SUPPLEMENTAL MATERIAL

APPENDIX

The other members of the ANOX study group are as follows: National Hospital Organization Kyoto Medical Center, Kyoto, Japan: K. Takabayashi, H. Ogawa, Y. Yamashita, Y. Hamatani, Y. An, Y. Tezuka, K. Doi, K. Kashiwabara, M. Murakami, S. Ieda, Y. Ueji, M. Mori, Y. Harada, K. Takahashi, D. Ishikawa, T. Nakayama, H. Oi, T. Hitano, T. Inoue, T. Shinagawa, M. Kimura, and A. Wada; National Hospital Organization Saitama National Hospital, Saitama, Japan: K. Matsumura, T. Katayama, Y. Miyabayashi, T. Sekine, N. Okada, and K. Namiki; National Hospital Organization Kure Medical Center, Kure, Japan: T. Kawamoto, R. Tamura, H. Nishiyama, O. Ichikawa, H. Kinoshita, T. Segawa, K. Yuasa, Y. Kimura, A. Kimura, M. Miura, and Y. Sumitani; National Hospital Organization Yokohama Medical Center, Yokohama, Japan: K. Iwade, Y. Seki, H. Hoshi, F. Mori, and K. Shimizu; National Hospital Organization Sendai Medical Center, Sendai, Japan: G. Ishizuka, N. Ogami, N. Yamaguchi, and H. Fujita; National Hospital Organization Kanazawa Medical Center, Kanazawa, Japan: E. Nakai and J. Arai; National Hospital Organization Hakodate National Hospital, Hakodate, Japan: S. Anzai, H. Hirose, K. Komuro, K. Shimastu, H. Yamada, and K. Inoko; National Hospital Organization Kobe Medical Center, Kobe, Japan: T. Okada, M. Kinugasa, J. Mukai, and A. Suzuki; National Hospital Organization Ehime Medical Center, Toon, Japan: T. Fujita and N. Izumi; National Hospital Organization Hokkaido Medical Center, Sapporo, Japan: H. Okamoto, T. Kaneko, J. Teranishi, M. Satoh, M. Fujita, H. Komatsu, H. Mutou, T. Akagami, T. Honma, A. Kikuchi, M. Kato, K. Otsu, and F. Suzuki; National Hospital Organization Sagamihara National Hospital, Sagamihara, Japan: M. Kanna, T. Dejima, M. Nakayama, S. Kikuchi, Y. Okajima, and H. Tanaka; National Hospital Organization Kyushu Medical Center, Fukuoka, Japan: K. Hiyamuta, K. Numaguchi, M. Nishihara, Y. Kuwabara, and S. Tanaka; National Hospital Organization Okayama Medical Center, Okayama, Japan: A. Ogawa and S. Watanabe; National Hospital Organization Tochigi Medical Center, Utsunomiya, Japan: T. Adachi, H. Sakurai, and H. Akutsu.

Data S1.

Supplemental Methods

Study population

Dyslipidemia was defined as a fasting low-density lipoprotein cholesterol of 140 mg/dL or more, high-density lipoprotein cholesterol of less than 40 mg/dL, triglycerides level of 150 mg/dL or more, or the use of lipid lowering drugs. Hypertension was defined as a clinic systolic blood pressure of 140 mm Hg or more, diastolic blood pressure of 90 mm Hg or more, or the use of anti-hypertensive drugs. Diabetes was defined as a fasting glucose of 126 mg/dL or more, glycosylated hemoglobin of 6.5% or more, or the use of oral hypoglycemic drugs or insulin. The presence of coronary artery disease (CAD), multi-vessel disease, and left main trunk disease was assessed using a modified American Heart Association/American College of Cardiology classification.[1] The severity of CAD was quantified using the Gensini score. [2]

Sample collection and biomarker measurement

The secondary predictors were vascular endothelial growth factor (VEGF), soluble vascular VEGF receptor-2 (sVEGFR-2) and two oxidatively modified low-density lipoproteins (LDLs), i.e. the α1-antitrypsin/LDL complex (AT-LDL) and serum-amyloid-A/LDL complex (SAA-LDL).

Fasting blood samples for serum were collected from the arterial catheter sheath at the beginning of coronary angiography. Serum (200 μL) was treated at 4°C for the measurements of AT-LDL and SAA-LDL, with the use of specific sandwich enzyme-linked immunosorbent assays (ELISA) (Ikagaku [now Health Sciences Research Institute West Japan], Kyoto, Japan).[3, 4] The remaining serum was stored at -80°C for a mean of 2 years until being assayed for other biomarkers. The serum levels of VEGF, sVEGFR-2, and high-sensitivity C-reactive protein (hs-CRP) were measured with specific, commercially available ELISA kits according to the manufacturers' instructions (Quantikine, R&D Systems, Minneapolis, MN, for VEGF, and sVEGFR-2; CycLex, MBL, Nagano, Japan for hs-CRP).[5]

The sensitivities of the assays for VEGF, sVEGFR-2, and hs-CRP were 5.0, 4.6, and 28.6 pg/ml, respectively. The inter-/intra-assay coefficients of variation (CV) of ELISA for VEGF, sVEGFR-2, and hs-CRP were <9%/<7%, ≤7%/<5%, and <6%/<4%, respectively. The sensitivity of the assay for N-terminal pro-brain natriuretic peptide (NT-proBNP) was 5 pg/mL, and the assay CV at values of the measuring range (5–35,000 pg/mL) was <10%. The sensitivity of the assay for contemporary sensitive cardiac troponin-I (cTnI) was 6 pg/mL, and the assay CV at the 99th percentile reference value of 40 pg/mL (potential range, 20–60 pg/mL) was <10%. The hemoglobin and the hematocrit levels, plasma hemoglobin A1c levels, and fasting serum levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, creatinine, and uric acid were

measured by routine methods.

Statistical analyses

The baseline clinical characteristics and outcome data are presented as means and standard deviations, medians and interquartile range, or number and proportions, as appropriate. The relationships between the baseline biomarker levels and the outcomes were investigated with the use of Cox proportional hazard regression in three sets of models: age- and sex-adjusted models; models adjusted for age, sex, traditional risk factors (dyslipidemia, hypertension, diabetes, and current smoking), obesity (defined as a body mass index of 25 kg/m^2 or more), chronic kidney disease (CKD) (defined as an estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2), a history of cardiovascular events (myocardial infarction, stroke, heart failure hospitalization, and coronary revascularization), CAD, multi-vessel or left main trunk disease, statin use, aspirin use, and anti-hypertensive drug use; models adjusted for established risk factors (age, sex, traditional risk factors, obesity, CKD, a history of cardiovascular events, CAD, multi-vessel or left main trunk disease, statin use, aspirin use, and anti-hypertensive drug use), and high levels of NT-proBNP, cTnI, and hs-CRP (for values above the cutoff points determined as previously reported).[6-8]

The necessary number of patients to treat in the present study was estimated on the basis of the association between the sVEGFR-2 level and cardiovascular events in a preliminary cohort study. In that study, a total of 513 patients were followed up over 3 years, and a total of 67 (13%) developed initial cardiovascular events. When the patients were divided into two groups using the optimal cut-off value determined by a receiver operating curve analysis, the event rates were 15.5% and 8.2%, respectively. Therefore, for 99% power and an alpha risk of 1% in the log-rank test for the Kaplan-Meier method, the minimum sample size was calculated as 955 and 1,039 in each group (1,994 in total). We estimated that the data of approximately 20% patients would be incomplete, and thus the target number of patients was 2,500.

Table S1. Baseline characteristics and incidence of outcomes.

Characteristic	Overall		Quartiles of VEGF-C (pg/mL)								*P* value *	*P* value for trend †
			Quartile 1 (388–2657)		Quartile 2 (2658–3543)		Quartile 3 (3544–4435)		Quartile 4 (4436–13801)			
	No.	Value	No.	Value	No.	Value	No.	Value	No.	Value		
Baseline characteristics												
Previous MI	2418	354 (14.6)	604	112 (18.5)	605	94 (15.5)	604	87 (14.4)	605	61 (10.1)	<0.001	<0.001
Previous PCI	2418	609 (25.2)	604	171 (28.3)	605	174 (28.8)	604	154 (25.5)	605	110 (18.2)	<0.001	<0.001
Previous CABG	2418	89 (3.7)	604	41 (6.8)	605	23 (3.8)	604	15 (2.5)	605	10 (1.7)	<0.001	<0.001
Previous CAD (MI, PCI, or CABG)	2418	701 (29.0)	604	208 (34.4)	605	194 (32.1)	604	176 (29.1)	605	123 (20.3)	<0.001	<0.001
Precious CHF hospitalization	2418	253 (10.5)	604	99 (16.4)	605	59 (9.8)	604	52 (8.6)	605	43 (7.1)	<0.001	<0.001
Previous stroke	2418	353 (14.6)	604	91 (15.1)	605	103 (17.0)	604	85 (14.1)	605	74 (12.2)	0.121	0.074
Family history of cardiovascular events	2418	691 (28.6)	604	176 (29.1)	605	155 (25.6)	604	165 (27.3)	605	195 (32.2)	0.068	0.181
Chronic kidney disease ‡	2418	999 (41.3)	604	336 (55.6)	605	291 (48.1)	604	207 (34.3)	605	165 (27.3)	<0.001	<0.001
Stage 3a		583 (24.1)		158 (26.2)		171 (28.3)		142 (23.5)		112 (18.5)		
Stage 3b		247 (10.2)		84 (13.9)		74 (12.2)		49 (8.1)		40 (6.6)		
Stage 4		83 (3.4)		34 (5.6)		26 (4.3)		13 (2.2)		10 (1.7)		
Stage 5		86 (3.6)		60 (9.9)		20 (3.3)		3 (0.5)		3 (0.5)		
Dialysis	2418	72 (3.0)	604	44 (7.3)	605	16 (2.6)	604	8 (1.3)	605	4 (0.7)	<0.001	<0.001

Table S1. Baseline characteristics and incidence of outcomes (continued).

Characteristic	Overall		Quartiles of VEGF-C (pg/mL)								*P* value *	*P* value for trend †
			Quartile 1 (388–2657)		Quartile 2 (2658–3543)		Quartile 3 (3544–4435)		Quartile 4 (4436–13801)			
	No.	Value	No.	Value	No.	Value	No.	Value	No.	Value		
Gensini score, median (IQR) §	2418	12.0 (2.5–36.0)	604	13.0 (3.0–42.0)	605	14.0 (3.5–36.5)	604	11.8 (2.5–34.0)	605	9.5 (0.0–32.5)	<0.001	<0.001
Systolic blood pressure, mean (SD), mmHg	2418	127 (18)	604	127 (19)	605	126 (19)	604	126 (17)	605	128 (19)	0.229	0.221
Diastolic blood pressure, mean (SD), mmHg	2418	71 (12)	604	68 (12)	605	69 (12)	604	72 (12)	605	73 (13)	<0.001	<0.001
Pulse rate, mean (SD), beats per minute	2418	70 (13)	604	71 (13)	605	70 (15)	604	70 (12)	605	71 (13)	0.531	0.941
LDL-cholesterol, mean (SD), mmHg	2366	105 (31)	590	95 (28)	599	102 (31)	585	107 (28)	592	114 (32)	<0.001	<0.001
HDL-cholesterol, mean (SD), mmHg	2353	54 (16)	585	54 (17)	592	54 (16)	584	56 (17)	592	54 (15)	0.098	0.999
Triglycerides, median (IQR), mg/dL	2382	111 (81–163)	594	99 (72–145)	598	113 (79–158)	592	109 (83–160)	598	131 (92–194)	<0.001	<0.001
Fasting glucose, median (IQR), mg/dL	2381	110 (96–142)	594	109 (95–140)	600	113 (97–143)	590	111 (95–144)	597	109 (97–140)	0.408	0.556
Hemoglobin A1c, median (IQR), %	2306	6.1 (5.6–7.0)	576	6.0 (5.6–6.9)	587	6.2 (5.7–7.0)	569	6.1 (5.7–7.1)	574	6.1 (5.7–7.1)	0.015	0.008
Creatinine, median (IQR), mg/dL	2418	0.9 (0.7–1.0)	604	0.9 (0.7–1.2)	605	0.9 (0.7–1.1)	604	0.8 (0.7–1.0)	605	0.8 (0.7–0.9)	<0.001	<0.001

Table S1. Baseline characteristics and incidence of outcomes (continued).

Characteristic	Overall		Quartiles of VEGF-C (pg/mL)								*P* value *	*P* value for trend †
			Quartile 1 (388–2657)		Quartile 2 (2658–3543)		Quartile 3 (3544–4435)		Quartile 4 (4436–13801)			
	No.	Value	No.	Value	No.	Value	No.	Value	No.	Value		
Estimated GFR, mean (SD), ml/min/1.73 m^2	2418	63 (22)	604	55 (25)	605	60 (21)	604	67 (20)	605	71 (20)	<0.001	<0.001
Hemoglobin, mean (SD), g/dL	2412	13.0 (1.8)	602	12.1 (2.0)	604	12.8 (1.8)	602	13.3 (1.5)	604	13.7 (1.6)	<0.001	<0.001
Hematocrit, mean (SD), %	2411	39.0 (5.3)	602	36.5 (5.8)	604	38.4 (5.1)	602	40.0 (4.4)	603	41.1 (4.8)	<0.001	<0.001
Uric acid, mean (SD), mg/dL	2347	5.9 (1.7)	579	6.0 (1.8)	593	6.0 (1.6)	586	5.8 (1.6)	589	5.9 (1.7)	0.129	0.191
VEGF, median (IQR), pg/mL	2418	248 (139–400)	604	151 (54–284)	605	255 (156–390)	604	279 (160–436)	605	319 (190–489)	<0.001	<0.001
sVEGFR-2, mean (SD), pg/mL	2418	6571 (1455)	604	6172 (1457)	605	6380 (1330)	604	6660 (1397)	605	7074 (1475)	<0.001	<0.001
SAA-LDL, median (IQR), μg/mL	2416	8.6 (5.6–15.0)	603	9.0 (5.1–15.9)	605	8.0 (5.8–16.0)	603	8.0 (5.1–13.6)	605	9.0 (6.0–16.0)	0.031	0.206
AT-LDL, median (IQR), μg/mL	2416	1.8 (1.5–2.3)	603	2.0 (1.5–2.5)	605	1.8 (1.5–2.3)	603	1.8 (1.5–2.2)	605	1.8 (1.5–2.2)	0.004	<0.001
Anti-hypertensive drug use	2418	1967 (81.3)	604	505 (83.6)	605	502 (83.0)	604	473 (78.3)	605	487 (80.5)	0.070	0.048
RASI	2418	1432 (59.2)	604	374 (61.9)	605	381 (63.0)	604	330 (54.6)	605	347 (57.4)	0.009	0.014
ACEI	2418	388 (16.0)	604	124 (20.5)	605	89 (14.7)	604	91 (15.1)	605	84 (13.9)	0.006	0.003
ARB	2418	1103 (45.6)	604	273 (45.2)	605	308 (50.9)	604	249 (41.2)	605	273 (45.1)	0.009	0.274
β-blocker	2418	715 (29.6)	604	207 (34.3)	605	176 (29.1)	604	159 (26.3)	605	173 (28.6)	0.020	0.017
Any lipid-lowering drug use	2418	1382 (57.2)	604	327 (54.1)	605	364 (60.2)	604	343 (56.8)	605	348 (57.5)	0.208	0.453
Any hypoglycemic drug use	2418	760 (31.4)	604	189 (31.3)	605	201 (33.2)	604	185 (30.6)	605	185 (30.6)	0.731	0.575
Oral hypoglycemic drugs	2418	603 (24.9)	604	149 (24.7)	605	155 (25.6)	604	148 (24.5)	605	151 (25.0)	0.972	0.975

Table S1. Baseline characteristics and incidence of outcomes (continued).

Characteristic	Overall		Quartiles of VEGF-C (pg/mL)								*P* value *	*P* value for trend †
			Quartile 1 (388–2657)		Quartile 2 (2658–3543)		Quartile 3 (3544–4435)		Quartile 4 (4436–13801)			
	No.	Value	No.	Value	No.	Value	No.	Value	No.	Value		
Insulin	2418	285 (11.8)	604	68 (11.3)	605	81 (13.4)	604	70 (11.6)	605	66 (10.9)	0.547	0.627
Any anti-platelet drug use	2418	1509 (62.4)	604	367 (60.8)	605	398 (65.8)	604	381 (63.1)	605	363 (60.0)	0.154	0.570
Any anti-coagulant drugs	2418	383 (15.8)	604	134 (22.2)	605	96 (15.9)	604	90 (14.9)	605	63 (10.4)	<0.001	<0.001
Warfarin	2418	332 (13.7)	604	115 (19.0)	605	84 (13.9)	604	82 (13.6)	605	51 (8.4)	<0.001	<0.001
Incidence of events, no. (/1000 person-years)												
All-cause death	2418	254 (37.5)	604	118 (73.4)	605	58 (33.9)	604	42 (24.4)	605	36 (20.7)	–	–
Cardiovascular death	2418	88 (13.0)	604	46 (28.6)	605	16 (9.3)	604	10 (5.8)	605	16 (9.2)	–	–
Myocardial infarction	2418	21 (3.1)	604	8 (5.0)	605	5 (3.0)	604	3 (1.8)	605	5 (2.9)	–	–
Stroke	2418	69 (10.3)	604	22 (13.9)	605	16 (9.5)	604	17 (10.0)	605	14 (8.2)	–	–
First MACE ||	2418	165 (24.7)	604	68 (42.9)	605	36 (21.4)	604	29 (17.1)	605	32 (18.7)	–	–

VEGF-C, vascular endothelial growth factor-C; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; IQR, interquartile range; SD, standard deviation; LDL, low-density lipoprotein; HDL, high-density lipoprotein; GFR, glomerular filtration rate; VEGF, vascular endothelial growth factor; sVEGFR-2, soluble vascular endothelial growth factor receptor-2; SAA-LDL, serum-amyloid-A/low-density-lipoprotein complex; AT-LDL, α1-antitrypsin/low-density-lipoprotein complex; RASI, renin angiotensin system inhibitors; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; MACE, major adverse cardiovascular event.

Values are expressed as number (percentage) unless otherwise indicated.

* The P value is for the comparison between groups, and is based on the chi-square test of independence for categorical variables, and the analysis of variance or Kruskal-Wallis for continuous variables.

† For continuous variables, the test for trend is based on linear contrast test with analysis of variance or Jonckheere-Terpstra test. For categorical variables, the test is based on the Cochran–Armitage trend test.

‡ Chronic kidney disease is defined as an estimated GFR of less than 60 ml/min/1.73 m^2 of body surface area. Estimated GFR of stages 3a, 3b, 4, and 5 are as follows: stage 3a, 45–59 ml/min/1.73 m^2; stage 3b, 30–44 ml/min/1.73 m^2; stage 4, 15–29 ml/min/1.73 m^2; stage 5, ≤14 ml/min/1.73 m^2.

§The Gensini score represents the angiographic severity of coronary artery disease employing a nonlinear points system for degree of luminal narrowing.

|| The MACE is defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

Table S2. Hazard ratios for all-cause death, cardiovascular death, and a major adverse cardiovascular event according to biomarker levels.

Biomarker and Criterion	Unadjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
All-cause Death								
VEGF	1.12 (1.01-1.24)	0.033	1.14 (1.03-1.26)	0.011	1.14 (1.03-1.26)	0.012	1.09 (0.98-1.21)	0.118
sVEGFR-2	0.79 (0.70-0.90)	<0.001	0.95 (0.82-1.09)	0.445	0.95 (0.83-1.10)	0.507	0.93 (0.81-1.06)	0.281
SAA-LDL	1.15 (1.07-1.24)	<0.001	1.14 (1.05-1.23)	<0.001	1.11 (1.02-1.20)	0.012	1.04 (0.96-1.14)	0.347
AT-LDL	1.30 (1.17-1.45)	<0.001	1.25 (1.12-1.39)	<0.001	1.24 (1.11-1.38)	<0.001	1.17 (1.04-1.31)	0.007
Cardiovascular Death								
VEGF	1.05 (0.86-1.27)	0.661	1.07 (0.88-1.29)	0.519	1.06 (0.87-1.29)	0.549	1.02 (0.83-1.25)	0.845
sVEGFR-2	0.78 (0.62-0.97)	0.025	0.89 (0.70-1.13)	0.352	0.92 (0.73-1.17)	0.507	0.92 (0.73-1.15)	0.455
SAA-LDL	1.12 (0.97-1.29)	0.125	1.11 (0.96-1.28)	0.156	1.07 (0.92-1.23)	0.376	1.00 (0.85-1.18)	0.996
AT-LDL	1.20 (0.99-1.45)	0.058	1.15 (0.95-1.40)	0.144	1.12 (0.92-1.36)	0.254	1.02 (0.84-1.24)	0.843
Major adverse cardiovascular event								
VEGF	1.08 (0.94-1.24)	0.255	1.09 (0.96-1.25)	0.185	1.09 (0.95-1.25)	0.217	1.06 (0.92-1.22)	0.428
sVEGFR-2	0.91 (0.78-1.07)	0.252	1.00 (0.85-1.19)	0.981	1.01 (0.85-1.19)	0.919	0.99 (0.84-1.17)	0.933
SAA-LDL	1.09 (0.97-1.22)	0.156	1.08 (0.96-1.22)	0.178	1.05 (0.93-1.18)	0.427	0.99 (0.87-1.13)	0.901
AT-LDL	1.17 (1.02-1.35)	0.026	1.14 (0.99-1.32)	0.064	1.13 (0.98-1.31)	0.094	1.06 (0.91-1.23)	0.445

HR, hazard ratio; CI, confidence interval; SD, standard deviation; VEGF, vascular endothelial growth factor; sVEGFR-2, soluble vascular endothelial growth factor receptor-2; SAA-LDL, serum-amyloid-A/low-density-lipoprotein complex; AT-LDL, α1-antitrypsin/low-density-lipoprotein complex. Values (for 1-standard deviation increase) were calculated with the use of multivariable Cox regression analyses. Data were adjusted for the following variables: model-1, age and sex; model-2, model-1 plus dyslipidemia, hypertension, diabetes, current smoker, obesity, previous cardiovascular events, chronic kidney disease, coronary artery disease, multi-vessel or left main trunk disease, statin use, aspirin use, and anti-hypertensive drug use; model-3, model-2 plus N-terminal pro-brain natriuretic peptide (>75th percentile), contemporary sensitive cardiac troponin I (>75th percentile), and high-sensitivity C-reactive protein (>1.0 g/mL).

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